

MCLEAN HOSPITAL IRB DETAILED PROTOCOL

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PROTOCOL TITLE

Neuroeconomics of Social Behavior Following Trauma Exposure

I. BACKGROUND AND SIGNIFICANCE

Significance

Impaired social functioning is a frequent and disabling sequela of trauma-related disorders. PTSD is associated with a high rate of severe impairment in quality of life (endorsed by 59% of patients) relative to other anxiety disorders, including panic disorder (20%), social phobia (21%), and OCD (26%) (Rapaport et al., 2005), with particularly marked impairment in social quality of life, $d = 1.53$ (Olatunji et al., 2007). Mounting evidence indicates that impairment in quality of life in PTSD is strongly related to its effect on social functioning (Charuvastra & Cloitre, 2008). Difficulties in interpersonal relationships are the problems that PTSD patients most frequently cite as their primary treatment goal (Rosen, 2013). In addition to being central, such difficulties are widespread and affect multiple social networks (Dutton et al., 2014), including marital relationships (Colman, 2004), and friendships and family relationships (Paunovic & Ost, 2004). Social impairments in PTSD fall into two major categories. The first involves socially disruptive externalizing behaviors and associated emotions, including anger, interpersonal violence, and aggression (Elbogen, 2014; Olatunji et al., 2010). The second involves social detachment, withdrawal, and isolation (Rosen, 2013). Social withdrawal, defined here in terms of reduced social network size, is of particular interest because of its strong relationship with health outcomes, including increased risk of disability (Mendes de Leon et al., 2001), reduced immune response (Pressman et al., 2005), and increased mortality risk (Shye et al., 1995); most critically, poor social integration is associated with a threefold increase in suicide risk (Tsai et al., 2015). Because women are at a 2.3-to-3-fold increased risk compared to men of developing PTSD following trauma (Breslau et al., 1997; Stein et al., 2000), understanding the differential neurobiological pathways that may contribute to the development of stress-related disorders in women is particularly critical. Women are more likely than men to endorse social detachment following trauma, especially when the trauma involves exposure to violence (Hourani et al., 2015). In this project, we propose abnormal reward processing (anhedonia) as a specific mechanism underlying social withdrawal in trauma-exposed women, and we present a paradigm that capitalizes on advances in neuroeconomics to elucidate the neural underpinnings of social withdrawal. Additionally, we propose to identify the possible influences of a stress peptide (pituitary adenylate cyclase-activating polypeptide: PACAP) implicated in sex-specific changes in social behavior following stress exposure. This contribution is expected to result in a number of tangible and important benefits. The first relates to assessment. By using a neuroeconomic paradigm to characterize a profile associated with social withdrawal following trauma exposure, it may become possible to develop methods to more quickly identify trauma-exposed individuals who are at particular risk for poor health outcomes including disability and mortality. The second tangible benefit relates to treatment. By identifying alterations in particular reward-related brain regions related to social withdrawal following trauma

exposure, we will identify possible future targets for neurobiological interventions.

Anhedonia as a core feature of PTSD.

Early models of reward functioning in depression and anxiety disorders proposed that hypoactivation of approach/reward systems (anhedonia) was a distinguishing feature of depressive disorders (Clark & Watson, 1991; Davidson, 1994). Perhaps in part because PTSD was classified as an anxiety disorder in DSM-IV, the importance of anhedonia in PTSD was underemphasized. However, a wealth of accumulating evidence indicates that anhedonia is a core feature in trauma-related disorders. This is reflected in the reconceptualization of PTSD outlined in DSM-5: “[m]any individuals who have been exposed to a traumatic or stressful event exhibit a phenotype in which, rather than anxiety- or fear-based symptoms, the most prominent clinical characteristics are anhedonic and dysphoric symptoms.” Several lines of evidence support this re-conceptualization emphasizing the centrality of anhedonia in PTSD. First, on self-report measures, PTSD is associated with decreased positive emotionality ($d = -1.91$; Frewen et al., 2012) and with increased hedonic deficits ($d = 1.88$, Frewen et al., 2012). Second, participants with PTSD show abnormal behavior on reward-based learning tasks (Sailer et al., 2008), including decreased key-pressing for primary rewards (Elman et al., 2005), lack of increased satisfaction after receiving unexpected rewards, and reduced satisfaction upon reward delivery (Hopper et al., 2008). Third, neuroimaging studies have identified abnormal neural responses to positive stimuli and reward in PTSD (Jatzko et al., 2006), including reduced nucleus accumbens (NAcc) and mPFC activity (Felmingham et al., 2014; Sailer et al., 2008). Fourth, recent factor analyses of DSM-5 PTSD symptoms support the importance of anhedonia in PTSD, suggesting that it is a separate factor from negative affect (Liu et al., 2014; Pietrzak et al., 2015). Directly relevant to the proposed research and highlighting the clinical importance of focusing on anhedonia, among all PTSD factors (including re-experiencing, avoidance, negative affect, anhedonia, externalizing behaviors, anxious arousal, and dysphoric arousal), anhedonia is the strongest predictor of quality of life and self-reported mental functioning, and is a significant predictor of depressed mood and suicidal ideation (Pietrzak, 2015). To summarize, there is strong empirical support for the claim that anhedonia is a prominent and important feature in PTSD. In spite of this clinical evidence, anhedonia in PTSD has received surprisingly scant attention in neurobiological research.

One potential explanation for the presence of anhedonia in PTSD is that it is attributable to comorbid disorders, including major depressive disorder (MDD) and/or substance use disorders. Estimates for comorbid MDD in PTSD samples reach the 50% range (Kessler et al., 1995; Rytwinski et al., 2013); comorbid alcohol abuse/dependence (51.9%) and drug abuse/dependence (34.5%) also are elevated (Kessler et al., 1995). Because anhedonia is a well-documented feature of MDD (Pizzagalli et al., 2008; Pizzagalli, 2014) and alcohol/substance use disorders (Corral-Frias et al., 2015; Franken et al., 2007), one could argue that this comorbidity accounts for anhedonia in PTSD. However, there is evidence that PTSD is associated with anhedonia even in the absence of or beyond these comorbid disorders. Specifically, PTSD patients with and without MDD endorse anhedonia at comparable rates: 67% in comorbid PTSD-MDD, and 63% in PTSD-only (Franklin & Zimmerman, 2001). Moreover, the aforementioned behavioral and fMRI abnormalities in reward processing persist even when analyses are restricted to non-depressed individuals with PTSD or recent substance use disorder (Felmingham et al., 2014; Hopper et al., 2008). Thus, there is substantial evidence that anhedonia is an important feature in PTSD even after accounting for effects attributable to comorbid disorders.

Reward processing, neural circuitry, and social withdrawal

There is growing acknowledgment of the key role of motivation/goal-directed behavior in shaping social interactions (Crick & Dodge, 1994). The subjective experience of social interaction can serve as a primary reward, recruiting mesolimbic reward circuitry in the same manner as other primary rewards (Pfeiffer et al., 2014). From a neurobiological perspective, anhedonia is conceptualized as a transdiagnostic phenomenon involving blunted reward circuitry responses (e.g. Corral-Frias et al., 2015).

This project focuses on three reward processing regions: the ventral striatum (VS), dorsal striatum (DS), and mPFC. The mPFC is involved in comparing the subjective values of rewards during decision-making (Kable & Glimcher, 2009; Plassman et al., 2010; Wang et al., 2014). The VS (including the NAcc and portions of the caudate and putamen: Haber, 2011) encodes the reward value of stimuli (Knutson et al., 2001; O'Doherty et al., 2002), while the DS (caudate and putamen) codes the reward value of responses (Balleine et al., 2007; O'Doherty et al., 2004). fMRI tasks requiring active reward-related decision-making may elicit DS rather than VS activity (Dichter et al., 2009; O'Doherty et al., 2004). Social anhedonia is associated with altered corticostriatal functional connectivity in both VS and DS (Wang et al., 2016). Similarly, hedonic deficits in VS and DS have both been identified using task-based fMRI in MDD (Pizzagalli et al., 2009). Abnormalities in reward processing circuitry can result in social disturbances (e.g., withdrawal) and increased risk for psychiatric disorders (Meyer-Lindenberg & Tost, 2012); reduced brain responsivity to social reward has been proposed to underlie social withdrawal in autism (Barman et al., 2015; Chevallier et al., 2012) and schizophrenia (Gromann et al., 2013). PTSD modeling in rats confirms the presence of an anhedonic subtype (28% of affected animals) involving altered NAcc and mPFC function and connectivity (Ritov et al., 2016).

Neuroeconomic reward hypothesis of social preferences.

In the present study, we propose to use a neuroeconomic game in order to capture altered social reward signaling in the VS, DS, and mPFC in trauma-exposed individuals. The use of economic games to probe social behavior in psychiatric disorders has been rapidly expanding. Importantly, these paradigms allow for formal operationalization of social emotions (Kishida & Montague, 2013). Economic exchange games use behavioral measures that are stripped of the complex environmental features that often accompany these emotions (King-Casas et al., 2005), and allow these processes to be assessed even when participants cannot articulate the underlying emotions (Zak, 2007). The neuroeconomic reward hypothesis of social preferences states that certain complex social behaviors such as non-selfish behavior and cooperation occur because these types of social interactions have special inherent hedonic or reward value, which is instantiated in brain regions including the VS, DS, and mPFC that encode the reward value of other types of primary reward (Behrens et al., 2008; Fehr & Camerer, 2007; Harris & Fiske, 2010; Insel, 2003; Izuma et al., 2010; Pfeiffer et al., 2014). Thus, neuroeconomic tasks can be used to identify the neural signals associated with social reward, and have already been robust and replicable in their ability to characterize social reward deficits across several disorders involving abnormal social behavior, including autism spectrum disorders (Chiu et al., 2008; Izuma et al., 2011), borderline personality disorder (King-Casas et al., 2005; King-Casas et al., 2008; Unoka et al., 2009), and psychopathy (Koenigs et al., 2010).

In this study, we will use the Trust Task to probe the neural signals underlying social anhedonia following trauma exposure. This paradigm is a particularly sensitive detector of altered social reward sensitivity in humans. In the task (Berg et al., 1995; King-Casas & Chiu, 2012; Kishida & Montague, 2013), one player is the 'investor,' and the second player is the 'trustee.' The investor is given an endowment and sends any amount to the trustee. Whatever portion the investor sends is multiplied, and the trustee can then opt to backtransfer any amount of the money to the investor. Critically, previous work has demonstrated DS responses consistent with a dopaminergic reinforcement learning signal, that are initially generated by the trustee when the partner's behavior is revealed (King-Casas et al., 2005; Kishida & Montague, 2013). This DS activity predicts subsequent increases in reciprocity and has thus been characterized as reflecting reward-related processing of a social gesture (Kishida & Montague, 2013), making it an ideal probe for detecting abnormalities in social reward processing. The Trust Task has previously been shown to be sensitive to abnormalities in social behavior. Participants with borderline personality disorder make lower investments, reflecting decreased reward value of the social interaction (Unoka et al., 2009; King-Casas et al., 2008). Similarly, compared to healthy controls, individuals with social phobia show reduced mPFC activity, again reflecting lower reward value for human interaction (Sripada et al., 2009). Trust game performance is sensitive to sex hormones and neuropeptides that play a central role in regulating social behavior, consistent with the notion that it captures critical features of

social reward (Boksem et al., 2013; Kosfeld et al., 2005; Bartz et al., 2011).

If trauma exposure results in blunting of sensitivity to social reward, then trauma-exposed individuals will demonstrate reduced prosocial behavior on neuroeconomic tasks, captured by behavioral abnormalities on the Trust Task. Reduced brain responsivity to social reward is a proposed mechanism underlying lower motivation to engage in social behavior in individuals with psychopathology (Barman et al., 2015; Gromann et al., 2013). Therefore, we hypothesize that, in trauma-exposed populations, the extent of social withdrawal (decreased social network size) will be predicted by alterations in both Trust Task social behavior and abnormal reward-related signaling in response to social cues on the Trust Task.

There are a few reports of altered Trust Task performance following trauma exposure. Lenow et al. (2014, 2015) found that assaulted adolescents showed altered responses to trust violations. Specifically, there were clusters in the DS and mPFC (as well as anterior cingulate and insular cortex) where the response to unexpected losses scaled with assault severity. This was a small, low-severity sample (15 assaulted girls, 3 with PTSD), and the task did not use real investment decisions. Cisler et al. (2015) used a multi-round trust game to identify behavioral abnormalities in women with PTSD ($n = 25$), including steeper decreases in trust and a slower return to baseline following trust violations. Parameters capturing trust game expectancies were related to neural activity in frontal regions on a different reward task. To summarize, there are encouraging initial demonstrations that neuroeconomic task behavior and neural responses are altered following trauma exposure. The proposed study would be the first fMRI study of Trust Task behavior in trauma-exposed adults and would further relate these findings to social anhedonia and social withdrawal, as well as to stress peptides.

PACAP: a stress-sensitive peptide

PACAP is involved in a variety of functional processes, including modulation of the HPA axis via regulation of corticotropin releasing factor (CRF). Its role in the stress response is demonstrated by animal literature indicating that: (1) chronic unpredictable stress results in increased PACAP in the bed nucleus of the stria terminalis (BNST), a major amygdala output pathway (Hammack et al., 2009); (2) infusion of PACAP into the amygdala or BNST produces stress-related behaviors (Hammack et al., 2010; Legradi et al., 2007); and (3) stress hormone synthesis in the HPA axis is PACAP-dependent (Stroth & Eiden, 2010). Human studies have further shown that in trauma-exposed women, but not men, higher PACAP levels are correlated with increased PTSD symptoms, an effect that persists even after controlling for depression ($r = 0.497$; Ressler et al., 2011). From a genetic perspective, a single nucleotide polymorphism (rs2267735) in the PAC1 receptor significantly predicts PTSD diagnosis in females (Almli et al., 2013; Ressler et al., 2011; Wang et al., 2013). Consistent with the role of PACAP in modulating fear circuitry, women who carry the PAC1 risk allele demonstrate reduced hippocampal activity during contextual fear conditioning (Pohlack et al., 2015) and increased amygdala and hippocampal activity in response to threat stimuli (Stevens et al., 2014). PACAP/ PAC1 receptor systems are modulated by estrogen in fear-sensitive regions (Ressler et al., 2011), highlighting that some portion of the increased risk for PTSD in women may be related to the effects of sex hormones (Shansky et al., 2010; Bangasser et al., 2010).

PACAP and social affiliation

Critically, animal work has implicated PACAP in social affiliation. PACAP knockout mice show increased social interaction, suggesting that PACAP regulates social withdrawal (Hattori et al., 2012). PACAP administration results in loss of approach behavior, but not increased fleeing, suggesting that it may be specifically related to social affiliation as opposed to social fear (Donahue et al., 2016). Similarly, PAC1-deficient female mice have abnormal initiation of affiliative behavior (Nicot et al., 2004). The specific mechanism by which PACAP affects social affiliation is currently unknown. Directly relevant to the proposed hypotheses, PACAP produces anhedonia in rats through pathways mediated by CRF (Dore et al., 2013).

Intriguingly, in mice, severe stress is associated with a loss of CRF's normal ability to increase dopamine release in the NAcc (Lemos et al., 2012). Additionally, while PACAP is prominently expressed in the hypothalamus, the NAcc has a high density of PACAP binding sites in rats (Masuo et al., 1992), raising the possibility that PACAP may directly act in the VS and alter reward processing. Though preliminary, this body of literature suggests that elevated PACAP levels may lead to a loss of social reward value through altered dopamine release in the VS. A significant limitation of the previous work on PACAP and social affiliation is that it has been conducted exclusively in rodents. This study would be the first attempt to demonstrate that increased PACAP levels are related to increased social anhedonia and social withdrawal in humans.

Summary

This study will use a neuroeconomic paradigm with state-of-the-art imaging protocols to probe abnormal social reward processing underlying social withdrawal in symptomatic trauma-exposed women. By also gathering self-report measures of social anhedonia, performance on non-social and social reward valuation tasks, and measures of real-world social functioning including social network size, we aim to specify how alterations in social reward processing result in social withdrawal and functional impairment. To our knowledge, PACAP has not previously been explored in relation to social behavior in humans, including trauma-exposed human populations. We will examine social withdrawal and reduced response to social reward on the Trust Task in relation to PACAP levels in trauma-exposed women.

II. SPECIFIC AIMS

Specific Aim 1: To identify a neurobehavioral profile on the Trust Task that predicts social withdrawal (decreased social network size) following trauma exposure. Compared to the posttraumatic spectrum-non-socially anhedonic (PTS-nonSA) group and the healthy control (HC) group, the posttraumatic spectrum-socially anhedonic (PTS-SA) group will demonstrate lower investments on the Trust Task than on the non-social risk task, as well as slower learning rates [**Hypothesis 1a**] and decreased reward-related responses during the outcome phase for social versus non-social rewards in the VS, DS, and mPFC [**Hypothesis 1b**]. Across the PTS groups, reduced VS, DS, and mPFC activity during the outcome phase of the Trust Task for social rewards will be associated with lower rates of investment on the Trust Task and smaller social network size [**Hypothesis 2**]. Within the PTS groups, decreased VS, DS, and mPFC response to social rewards will mediate the relationship between social anhedonia and reduced social network size [**Hypothesis 3**]. PTS individuals with higher self-reported social anhedonia and social withdrawal also will show reduced VS-mPFC connectivity for social rewards on the trust task [**Hypothesis 4**].

Specific Aim 2: To identify a potential biomarker that predicts social anhedonia and social withdrawal following trauma exposure. We propose to examine social withdrawal and reduced response to social reward on the Trust Task in relation to PACAP levels in trauma-exposed women. Elevated PACAP levels will be associated with lower investments on the Trust Task, decreased social reward signals during the outcome phase for social rewards in the VS, DS, and mPFC, and smaller social network size [**Hypothesis 5**].

III. SUBJECT SELECTION

PHASE 1 (Establishing Trust Task trustee database)

Phase 1 will involve recruiting healthy volunteers (n = 60) to complete the Trust Task in order to establish a database of trust task responses from anonymous healthy trustees.

Inclusion criteria: Age 18-45, self-reported healthy volunteer status

Exclusion criteria: 1) inability to provide written informed consent in English; 2) inability to see task due to vision impairments.

Participants who produce T-scores of 65 or higher on any Brief Symptom Inventory (BSI) subscales will not be eligible to remain in the Trust Task participant pool.

Sources of subjects and recruitment methods:

Recruitment sources will include:

- 1) Healthy participants from other research studies at McLean Hospital in Belmont, MA
 - a. I plan to collaborate with other investigators at McLean Hospital who will ask their healthy participants if they would be interested in participating in an additional study which will take approximately 1/2 an hour to complete. Should they consent, the participants will stop by our lab following the completion of the other investigators' studies, receive the consent form for the present study, and complete the protocol for Phase 1 participation.
 - b. I anticipate collecting Phase 1 data from up to 60 healthy participants (in order to obtain usable data from 50 participants after accounting for data loss).
- 2) Healthy adults at McLean Hospital in Belmont, MA.
 - a. We plan to recruit healthy adults at McLean Hospital by putting up flyers around campus, asking if healthy adults would be interested in participating in a study which will take approximately 1/2 an hour to complete. Should they consent, the participants will stop by our lab, receive the consent form for the present study, and complete the protocol for Phase 1 participation.
- 3) Healthy community-based volunteers. We plan to recruit healthy adults through craigslist postings, through the procedures described above in (2).
- 4) Former Phase 1 participants in protocol 2016P000978. Participants in Phase 1 in that prior study completed procedures identical to those in this study (BSI, Trust Task). We plan to recontact participants who provided permission to be recontacted and who meet inclusion criteria for this study's Phase 1 pool (age 18-45, BSI T-scores under 65, produced usable Trust Task data). We will send them a consent form by mail asking for their permission to include them in this study's Phase 1 participant pool.

PHASE 2 (Main study phase)

Inclusion criteria: female, trauma exposure appropriate to group, for trauma-exposed groups the index trauma is actual or threatened physical assault or sexual violence, PCL-5 score 33 and above (for PS-SA and PS-nonSA groups), right handedness, age 18-45, English as a first language.

Exclusion criteria: history of neurological illness (including head injury with loss of consciousness > 5 minutes), medical conditions that may influence neuroimaging (e.g. HIV), current or past DSM-5 Axis I disorder (for HC group), history of bipolar disorder or schizophrenia spectrum disorder, contraindications for MRI, alcohol dependence in the past 5 years, substance dependence in the past 3 years, daily substance use in the past year, prescribed psychotropic medication use in the past month, Wechsler Abbreviated Scale of Intelligence- Second Edition (WASI-II) FSIQ < 70.

Sources of subjects and recruitment methods: This project compares three groups: posttraumatic spectrum-socially anhedonic (PTS-SA, n = 36), posttraumatic spectrum-non-socially anhedonic (PTS-nonSA, n = 36), and healthy controls (HC, n = 36). Participants will be recruited from the following sources: 1) Recruiting new participants from the Boston metropolitan area through newspaper

advertisements, flyers, Internet websites, and word of mouth. 2) Recontacting participants who have recently participated in one of this lab's studies and who previously expressed interest and provided written consent to be re-contacted about additional studies. Specifically, these are subjects who have participated in: Dr. Isabelle Rosso's IRB-approved protocols entitled "Cerebral GABA and Fear Conditioning in PTSD" (protocol # 2012P001237) and "An investigational study of riluzole effects on hippocampus biomarkers" (protocol #2016P002687); Dr. Scott Rauch's IRB-approval protocol entitled "Internet-Based Cognitive Behavioral Therapy Effects on Depressive Cognitions and Brain Function" (protocol # 2012P000131); Dr. Elizabeth Olson's IRB-approved protocol entitled "Reward valuation in posttraumatic stress disorder: contribution of nucleus accumbens-insula circuitry" (protocol # 2016P002890). These subjects will be re-contacted by phone or email, using contact information that they previously provided.

IV. SUBJECT ENROLLMENT

PHASE 1 (Establishing Trust Task trustee database)

As previously discussed, Phase 1 participants will be healthy adults at McLean Hospital. Should these participants agree to participate in the present study, they will be invited to stop by the laboratory either immediately preceding or following their participation in the other investigators' studies, if applicable.

Then, written informed consent will be obtained upon subjects' arrival on their first visit to the present study. An investigator will sit down with subjects and review the consent form, discussing its contents, including the study procedures involved, the potential risks and benefits to participating, and the voluntary nature of participation. Subjects will be told that they can discontinue their participation at any time. Subjects will then be given as much time as they want to read through the consent form in detail. They will be given the opportunity to ask questions, and to consult with their friends, family members, or doctors if they wish. If desired, a subject may take the consent form home in order to discuss it with others, or in order to take more time to decide whether to participate. Once subjects have read the consent form, have had all their questions answered, and have agreed to participate in the study, they will initial the bottom of each page and sign/date the final page. They will be given a copy of the consent form for their records.

The informed consent will typically be collected by a research assistant trained by the P.I., or, in some cases, by the P.I.

Remuneration

Healthy control participants who participate in the initial phase of Trust Task development will be compensated as follows. They will not be paid directly for the brief study visit (consisting of consent, BSI, and Trust Task). Rather, their responses to possible Trust Task offers will be recorded, and they will be paid in the future based on Phase 2 participant responses. After each Phase 2 participant completes the Trust Task, one trial will be randomly selected. For example, if Trial #13 is selected, and Trial #13 involved an offer of \$6 from the Phase 2 participant, then the Phase 1 participant's pre-recorded decision to share or keep that offer will be used to determine remuneration for the Phase 1 and Phase 2 participants. If the Phase 1 participant chose to share the offer, then the quadrupled amount (\$24) is split 50-50 (\$12 to the Phase 1 participant; \$12 to the Phase 2 participant). If the Phase 1 participant chose to keep the offer, then the quadrupled amount (\$24) goes to the Phase 1 participant only (\$24 to the Phase 1 participant; \$0 to the Phase 2 participant). Because of the random nature of the drawing, it is not possible to determine in

advance the exact amount of compensation that each Phase 1 participant will receive. The possible range of task-related compensation starts at \$0. In the extremely unlikely event that the same Phase 1 participant trial was randomly selected for every Phase 2 participant (n = 40), and that trial involved the maximum possible payout to the Phase 1 participant (\$40), it is conceptually possible that a single Phase 1 participant could earn up to \$1600. The likely estimate of compensation for Phase 1 is approximately \$50. If a Phase 1 participant was never randomly selected to receive a payout, he or she will be compensated \$5 for his/her time at the conclusion of the study. All Phase 1 payments will be made by mail.

Phase 1 participants who produce T-scores of 65 or higher on any Brief Symptom Inventory (BSI) subscales will not be eligible to remain in the Trust Task participant pool. They will be paid \$5 by mail at the end of the study.

PHASE 2 (Main study phase)

Methods of enrollment, include procedures for patient registration and/or randomization

Participants' initial study contact will be a phone call wherein they will receive a preliminary description of the study. During this phone call, a research assistant or other study investigator will convey general information about the research study (e.g., general aims, location, duration and remuneration), and specific information about the procedures (i.e., type and duration of procedures). They will be asked to complete a telephone pre-screening questionnaire (if they have not already done so) to establish whether they meet entry criteria on the PCL-5 and RSAS. Participants meeting these criteria will continue with the telephone screen. Subjects will also be asked a number of screening questions to determine whether they meet the basic selection criteria (see Telephone Screen). After this exchange of initial information, subjects will be invited to think about whether they would like to participate in the study. If they express interest in participating, they will be scheduled for the study visit. If they request more time to consider the decision of whether or not to enroll, they will be provided a phone number to call back with a decision (and/or to ask any questions).

Procedures for obtaining informed consent (including timing of consent process)

Written informed consent will be obtained upon subjects' arrival. An investigator will sit down with subjects and review the consent form, discussing its contents, including the study procedures involved, the potential risks and benefits to participating, and the voluntary nature of participation. Subjects will be told that they can discontinue their participation at any time. Subjects will then be given as much time as they want to read through the consent form in detail. They will be given the opportunity to ask questions, and to consult with their friends, family members, or doctors if they wish. If desired, a subject may take the consent form home in order to discuss it with others, or in order to take more time to decide whether to participate. Once subjects have read the consent form, have had all their questions answered, and have agreed to participate in the study, they will sign/date the final page. They will be given a copy of the consent form for their records.

The initial phone screen and informed consenting generally will be conducted by a research assistant who has been trained on both procedures by the P.I., or in some cases by the P.I. After conducting a phone screen, the research assistant will review information with the P.I. to confirm whether or not the prospective subject meets initial entry criteria and should be scheduled for a study visit.

Remuneration

Participants who complete the entire study will receive \$200 to cover the anticipated eight hours of time for study participation. Partial completion of the study will be remunerated at the pro-rated rate of \$25 per hour for procedures that are completed. Additionally, participants will be compensated for one randomly selected Trust Task trial (average anticipated payout per participant: \$20).

V. STUDY PROCEDURES

Phase 1

Study visits and parameters to be measured

The present study involves a single visit to McLean Hospital, during which we will obtain measures of trust task behavior and general psychopathology.

Procedures

Neuroeconomic Game

The paradigm will be a multiple single-shot trust task (Stanley et al., 2012). Each participant will play the game as trustees. Players' decisions to all possible offers will be recorded and stored in a database to be used in participants' task completion during Phase 2. On each trial, the trustee will decide to 'share' (50-50) or 'keep' (100% to trustee) each amount displayed. Real payments for one randomly selected trial will be delivered by mail (to the trustee).

Brief Symptom Inventory

All subjects will also complete the Brief Symptom Inventory, a 53-item self-report inventory of general psychological functioning and psychopathology. This will be administered by a research assistant or other study investigator familiar with its content.

PHASE 2 (Main study phase)

The study will require one visit. Briefly, this will include diagnostic interviews to establish eligibility, questionnaires and cognitive tasks, a 1-hour MRI scan including task-based fMRI, and a blood draw for analysis of PACAP and related hormone levels.

Screening procedures (SCID-5, CAPS-5, WASI-II) will establish eligibility. Participants will then complete additional questionnaires and the fMRI scan (see below), playing the repeated, single-shot trust game inside the scanner.

Procedures

Psychiatric Interview and Symptom Scales

Once subjects understand all study procedures and have provided written consent, they will undergo a structured psychiatric interview, namely the Structured Clinical Interview for DSM-5 (Research Version: SCID-5-RV) and the SCID-5-PD. In addition, PTSD group participants will complete the Life Events Checklist for DSM-5 and Clinician-Administered PTSD scale for DSM-5 (CAPS-5) in order to quantify trauma exposure and symptom severity. The clinical instruments will be administered by Dr. Olson, who is a licensed psychologist with training and experience in these measures.

Questionnaires: Edinburgh Handedness Scale, PTSD Checklist (PCL), Traumatic Life Events Questionnaire (TLEQ), Adverse Childhood Experiences scale (ACE), NEO Personality Inventory, Beck Depression Inventory, Second Edition (BDI-II), Empathy Quotient (EQ), Social Network Index (SNI), Dunbar's number (Dunbar & Spoons, 1995: List the initials of everyone with whom you had some kind of

social contact within the last 30 days). We also will administer an in-house Information Questionnaire with questions regarding recent health habits (sleep, eating, substance use, etc.). Questionnaires will be administered by a research assistant or other study investigator familiar with their content.

Urine Toxicology

Once subjects have provided informed consent and have met study selection criteria based on results of the interviews, they will be asked to provide a urine sample under the supervision of a research assistant. This sample will be tested for cannabinoids, ethanol, amphetamines, opioids, phencyclidine, barbiturates, benzodiazepines, and cocaine metabolites (Triage® Drugs of Abuse Panel: Immediate Response Diagnostics, San Diego, CA). Female subjects will be informed that their sample will also be used to confirm negative HCG status (QuPID One-Step Pregnancy, Stanbio Laboratory, Inc., San Antonio, TX).

Imaging Procedures

Prior to scanning, subjects will complete standard McLean MR safety screening, including filling out the McLean Imaging Center questionnaire that queries about past surgeries and metallic implants that may be contraindicated for MR. An MR technician will review this information prior to taking the subject into the magnet room. During scanning, subjects will be given earplugs to reduce the noise made by the magnet, and subjects will also be given headphones through which they can communicate with the technologist and research staff at any time. Head and back support will be provided to minimize discomfort.

All subjects will undergo high-resolution structural and functional MRI on a 3T Siemens Prisma (Siemens Medical Solutions USA Inc., Malvern, PA), whole-body, clinical MR system using a 64 channel phased-array design RF head coil operating at 123 MHz. Once participants are positioned inside the bore, a three-plane series of scout images will confirm optimal positioning. Then three series of anatomical whole-brain images will be acquired, namely i) high-contrast T₁-weighted MPRAGE images (using parameters optimized for morphometric analysis using Freesurfer software: 128 slices, 2562 matrix, echo time= 2.7ms; repetition time= 2730 ms; inversion time= 1000ms; flip= 7°, slice thickness= 1.33mm), ii) FLAIR and iii) fast spin-echo (FSE) T₂-weighted image sets. Anatomical scans will be reviewed by a board-certified radiologist. If a clinical abnormality is detected, the subject will be excluded from the study, and the subject's physician will be notified upon written release.

fMRI Acquisition and Analysis: MRI data will be acquired on a 3T Siemens Prisma with a 64-channel head coil. Gradient echo T₂*-weighted echoplanar images will be acquired using the University of Minnesota multi-band BOLD EPI sequence (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013), which achieves excellent temporal and spatial resolution (TR/TE: 1300/35ms; FOV: 224 mm; matrix: 64X64; 78 slices; in-plane resolution: 2mm; voxels 2 x 2 x 2mm, multiband factor of 6). The EPI acquisition will use prospective motion correction.

Neuroeconomic Game (fMRI task): Multiple, single-shot Trust Task (Stanley et al., 2012). Participants will play as investors against real anonymous trustees, drawn from a pool of minimally screened participants (Brief Symptom Inventory). Trustees' decisions to all possible offers will be pre-recorded in a database. Prior to the task, the investor will receive an endowment of \$30. On each trial, the investor will choose to send the trustee \$0-\$10 (increments of \$2). The amount sent will be quadrupled, and the trustee's decision to 'share' (50-50) or 'keep' (100% to trustee) will be displayed. The game will be played as single shots with 50 trustees. Real payments for one randomly selected trial will be delivered in person (to the investor) or by mail (to the trustee). There also will be a non-social risk game in which the decisions are computer-generated. We will use computational modeling (Rescorla-Wagner model) to derive the learning rate (Cisler et al., 2015). Following completion of the Trust Task, one trial will be randomly selected for real payout.

If time permits, diffusion tensor imaging (DTI) images also will be acquired (TR= 7300 ms, TE = 80 ms, 72 diffusion directions, b = 1000).

PACAP Analysis

There will be 1 blood draw which will require 9mL of blood, equivalent to approximately 2 teaspoons. Plasma will be collected in EDTA collection tubes, iced immediately, centrifuged, and stored in a -80C freezer. PACAP38 (38-amino acid peptide form) will be quantified via radioimmunoassay by the Ressler lab (detailed methods: see Ressler et al., 2011). PACAP activity is influenced by estradiol and luteinizing hormone (LH) (Park et al., 2010; Ressler et al., 2011). We will control for this by running participants only during cycle days 1-6 and by covarying estradiol, LH, and progesterone levels in PACAP analyses.

VI. BIOSTATISTICAL ANALYSES

Hypothesis 1: 1a) Given that increased social anhedonia will be associated with decreased reward value for social interactions, we hypothesize that, compared to the PTS-nonSA and HC groups, the PTS-SA group will demonstrate lower investments and slower learning rates on the Trust Task than on the non-social risk task compared with PTS-nonSA and HC subjects. No differences are anticipated between the HC and PTS-nonSA groups. 1b) The HC and PTS-nonSA groups will show greater VS, DS, and mPFC responses during the outcome phase of the trust game for 'share' versus baseline, compared to the PTS-SA group, for the real partner condition (Trust Task), but not for the risk task. Using SPM12, first-level analyses will contrast the hemodynamic response to trials involving the revelation of the partner's decision to share versus baseline, thus capturing the VS, DS, and mPFC signals associated with positive social interactions. At the second level, groups will be contrasted controlling for age. A priori hypotheses will be evaluated using ROIbased analyses, which will be complemented by whole-brain analyses (familywise error corrected). All analyses will be performed with and without self-reported race/ethnicity as a covariate to identify possible confounds related to this factor. We will control for age and smoking status, due to effects on dopamine functioning.

Hypothesis 2: Because social withdrawal will occur in response to reduced social reward value, we hypothesize that across the PTS groups, reduced VS, DS, and mPFC activity during the outcome phase of the trust game for 'share' outcomes will be associated with lower Trust Task investments, greater self-reported social anhedonia, and smaller social network size. At the second level, multiple regression will be performed using self-reported social anhedonia as a continuous covariate of interest; decreased VS, DS, and mPFC response to positive social interactions will correlate with increased social anhedonia, after controlling for age and total CAPS-5 score.

Hypothesis 3: Within the PTS groups, decreased VS, DS, and mPFC response to 'share' outcomes will mediate the relationship between social anhedonia and reduced social network size. Mediation analyses will be conducted via bootstrapping using the PROCESS Macro (Hayes, 2013) in SPSS.

Hypothesis 4: Because increased VS-mPFC connectivity is associated with increased reinforcement learning rates (van den Bos et al., 2012), we predict that PTS individuals with higher self-reported social anhedonia and social withdrawal will show reduced VS-mPFC connectivity for social rewards on the Trust Task. Using SPM12, a whole-brain psychophysiological interaction (PPI) analysis will be conducted using the VS as the seed region of interest. The seed time course will be entered as a regressor into the GLM, and the interaction (PPI) regressor will be generated. Task and seed ROI regressors will be covaried out to identify voxels where the VS time course has a stronger relationship for social reward versus baseline.

Hypothesis 5: Finally, we hypothesize that elevated PACAP levels will be associated with lower

investments on the Trust Task; decreased social reward signals during the outcome phase for ‘share’ outcomes in the VS, DS, and mPFC; and smaller social network size.

Power Analysis

Compared to controls, the effect size for alterations in social behavior following trauma exposure is large ($d \geq 1.0$: Olatunji et al., 2007, 2010). The effect sizes for altered neuroeconomic task performance following trauma exposure are medium to large ($d = 0.783$: Lenow et al., 2014; $d = 0.972$: Cisler et al., 2015), while the effect sizes of altered responsivity in the striatum and mPFC in trauma exposed populations are in the medium range ($d = 0.576-0.773$: Sailer et al., 2008). In women, correlations between PACAP levels and PTSD symptoms are large ($r = 0.497$: Ressler et al., 2011). While the Trust Task has not previously been used in women with PTSD, Sripada et al (2009) compared individuals with social anxiety disorder to healthy controls and found a large group difference for social vs non-social reward in the mPFC ($d = 0.854$). Assuming 15% unusable data, we propose to enroll 36 PTS-SA, 36 PTS-nonSA, and 36 HC participants, resulting in usable data from 30 subjects per group, resulting in power > 0.90 to detect group differences. This is comparable with other neuroeconomic neuroimaging studies (e.g. Kirk et al., 2011: $n = 26$ in group 1; $n = 40$ in group 2).

VII. RISKS AND DISCOMFORTS

Foreseeable Risks and Discomforts

MR Scanning

MR does not use ionizing radiation. In a small percentage (less than 5%) of subjects, feelings of claustrophobia may be experienced while in the scanner, although self-reported claustrophobia will be an exclusion criterion (queried during the telephone screen and psychiatric interview). Participation in an MR study does require subjects to be exposed to strong magnetic fields, the long-term effects of which are unknown. The magnetic fields also require caution given the risk of attraction of ferromagnetic metal objects by the high strength magnetic field. Significant risks exist for anyone with metal in their body (e.g., shrapnel, pacemaker), requiring exclusion of these subjects from study participation. In addition, some subjects find the scanning experience unpleasant because of the noise of the scanner during acquisition. In rare cases, a very slight, uncomfortable tingling of the back is induced in some people. These risks are the same as those present for a clinical MR scan, and are not increased by the research project described herein.

Clinical Interview

It is possible that during the structured clinical interview or rating scales, subjects may become distressed when recalling periods of their lives or their current mood state. This can certainly be foreseen for PTSD patients recounting their traumatic experiences. Since Dr. Olson has been conducting these interviews with PTSD subjects in other studies over the past several years, she has found it useful to plan longer time-slots for interviews with PTSD patients, thereby allowing the interview to go at each subject’s pace, taking a break if needed, and/or offering a glass of water or other “grounding” pause as needed. None of the PTSD subjects interviewed thus far (at least 40) have reported excessive distress or undue consequences, and none have been unable or unwilling to complete the clinical interview.

Trust Task

No risk or discomfort is expected due to the process of completing of this task, however, participants may feel mildly frustrated or disappointed about the outcome.

Procedures for Minimizing Risks

First and foremost, subjects will be informed that they may terminate their study participation at any time, for any reason. In addition, the following will be enforced:

Minimizing Subject Burden

Subjects who underwent a clinical anatomical MRI at McLean within the past year will not need to repeat this scan to be read by the radiologist, as per hospital policies.

MR Scanning

A number of precautions will be taken to mitigate any possible adverse consequences of participating in the scanning protocol. Subjects are interviewed prior to entering the study and specifically queried about implanted metal objects and other MR contraindications by trained MR technicians. Following manual demetallizing by trained personnel, all subjects pass through a metal detector wand prior to entering the scanning room to ensure no stray material has been overlooked. Noise from the gradients is minimized by using earplugs and gradient dampening headphones (Resonance Technology). Subjects can communicate easily with study personnel through the microphone integrated in their headphones, and can stop the scan at any time by squeezing a panic button. Subjects who appear to be claustrophobic or are unable to be made comfortable will be removed from the scanner immediately and assessed for stability.

Clinical Interview

Subjects will be informed that responding to interview questions is voluntary, and that they may decline to answer any question. Subjects who decline the interview or any other study procedures will be compensated in proportion with their study participation time. As described above, care is taken to conduct the interviews at a rate comfortable for subjects, offering breaks as needed.

Trust Task

One risk of this task is that participants may feel mildly frustrated or disappointed about the outcome. This risk will be minimized by: 1) reminding participants during consent that a variety of financial outcomes are possible, including the possibility of not winning much money; 2) allowing participants an extra break if they are mildly frustrated or disappointed following the task. We do not anticipate that participants will be more severely frustrated or angry, but if this occurs, we will remind them that their participation is completely voluntary and that they may withdraw from participation at any time.

Blood Draws

A blood draw may lead to a small arm bruise and, in rare cases, clot or infection at the site the blood was drawn. Some people become light-headed during or immediately after a blood draw. These are rare occurrences and in our experience vast majority of subjects tolerate blood draws well. Subjects will be monitored for 15 minutes following the blood draws to ensure they are doing well.

Confidentiality

All subjects will be informed of confidentiality laws (and limits to confidentiality). Confidentiality of information collected will be maintained with the assignment of subject identification numbers, which will be used in place of subject names in all data spreadsheets, questionnaires and other forms and reports. Coding schemes showing the assignment of identification numbers to subject names will be stored in locked cabinets at the CDASR. All computerized databases with identifying information will be password-protected. All of the data collected will be kept for a minimum of seven years after study completion. Onsite access to study data will be limited to the McLean investigators and their staff; any sharing of data with external collaborators or entities that analyze the data will be controlled by the investigators of this study.

All subjects will complete MR imaging at McLean Hospital, requiring assignment of a medical record number (MRN) for archival purposes. MRNs are generated by a hospital computer database that is only accessible by authorized McLean clinical staff. A master list of MRNs with corresponding subject numbers will be kept in locked and password-protected files. For clinical scans, which are read and

interpreted by a board-certified radiologist, identifying information such as first and last name and date of birth also is required per standard hospital policies. All other data and forms derived from the study will be coded only with the subject's study ID number (not MRN) and kept in locked and password-protected files. Subjects' names (or other PHI) will not appear on assessment measures or other data entry forms.

VIII. POTENTIAL BENEFITS

Potential benefits to participating individuals

There are no anticipated direct benefits to individual subjects for participating in this study. That is, for the majority of subjects the research data collected are not expected to be personally beneficial to them. We have found, however, that some PTSD subjects find it beneficial to learn more about their symptoms (e.g., learning that concentration problems can be a symptom of PTSD by virtue of participating in the interview). In addition, some subjects may derive future benefit from the clinical MRI scan. Every subject's MRI scan is read and interpreted by a clinical neuroradiologist and kept on file permanently at McLean Hospital. This allows individuals to have a baseline MRI scan at no charge, which may be accessed by their physicians or other medical persons should the need arise.

Potential benefits to society

This study will provide novel information on neural mechanisms involved in alterations in reward valuation in Posttraumatic Stress Disorder. This may lead to improved behavioral therapies targeting specific symptoms of a common and debilitating brain disorder that is currently difficult to treat.

IX. MONITORING AND QUALITY ASSURANCE

Data Monitoring

The study investigators will be directly responsible for monitoring the data collection, data coding and processing, and continual adherence to the IRB-approved protocol. This will be feasible given that the study involves low/minimal risk to a manageable number of subjects, and that all data collection and storage will take place at a single site. Moreover, the investigators have thorough understanding and knowledge of all the procedures and data being collected (neuroeconomic data, demographic data, psychiatric data). The validity and integrity of the data will be ensured by having each type of data collected and/or supervised by an investigator with relevant expertise: collection of all psychiatric data will be performed and supervised by Dr. Olson, a clinical psychologist. All subject staff will receive thorough explanations of all procedures, even those in which they may not be directly involved. The P.I. and investigators will conduct quality control checks after every five enrolled subjects, including: 1) review all forms and test/interview results, and enter data into spreadsheets; 2) ensure that the different subject groups are being recruited with the selection and matching criteria dictated by the scientific aims; 3) verify that all data are collected and analyzed per protocol privacy and confidentiality policies (see next section); 4) conduct interim processing and analyses of neuroeconomic task data to ensure that high-quality data are being collected, justifying continued collection of data.

Any access to de-identified data by external research collaborators will be controlled by the investigators of this study.

Safety Monitoring

The investigators will be responsible for safety monitoring, overseen by the P.I. This study involves minimal/low risk to subjects: 1) the psychiatric questionnaires do not involve safety risks *per se* but can be uncomfortable or distressing; in addition, appropriate measures will be taken if subjects are deemed to present a safety risk to themselves or others; 2) the neuroeconomics task does not pose any foreseeable risks or discomforts beyond possible mild frustration or disappointment.

1) Questionnaires and Cognitive Tasks

Prior to beginning the psychiatric symptom scales, we will remind subjects that their participation is voluntary and that they may decline to answer any question(s). If a subject experiences extreme distress during the completion of questionnaires, the overseeing study staff member will discontinue the study participation for that subject.

If a subject endorses symptoms of active suicidality, including endorsement of suicidality (score of 1, 2, or 3) on the BDI-II Question 9, the subject will be evaluated by a licensed doctoral-level clinician via an immediate in-person assessment. The doctoral-level clinician will use his/her professional judgment to determine whether continued involvement in the study is appropriate, and the subject will be provided a list of resources for treatment, including medication and/or face-to-face therapy, if warranted. During face-to-face meetings, subjects judged to be at imminent risk for self-harm will be escorted to McLean Hospital's Clinical Evaluation Center (CEC) where they will be evaluated for inpatient admission. Similarly, immediate in-person assessment and triage will be conducted by a licensed doctoral-level clinician in the unlikely event that a subject reports a threat to an identifiable third person.

2) Neuroeconomics Task

We will remind subjects that their participation is voluntary and that they may decline to complete the neuroeconomics task if they wish.

Adverse event reporting guidelines

Any adverse events will be reported to the Partners Institutional Review Board by the P.I. Reporting will follow the guidelines established by Partners Healthcare (http://healthcare.partners.org/phsirb/adverse_events.htm) for reporting of adverse events based on their seriousness, unexpectedness, and relatedness to the research procedures. As a general policy, any adverse event will be reported as soon as possible after the P.I. first becomes aware of it.

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